

# Working group on in-silico reference files



I-SRF

Summary of Themes

## Launching a working group to explore expanded use of in-silico reference files in molecular diagnostics

Biomarkers and next-generation sequencing (NGS) tests have become pivotal in the diagnosis and treatment of diseases. Recent data shows, for example, increasing use of biomarker testing by oncologists.<sup>1</sup> NGS testing is not only increasingly prevalent but also complex: today, large-scale gene panels can survey hundreds or even thousands of genes to provide critical insights about a patient's health and inform treatment decisions.

These trends come at a time when the regulatory landscape in the United States for overseeing diagnostic tests remains in flux,<sup>2</sup> with diverse stakeholders opining on the optimal oversight approach for diagnostic tests. In the absence of an updated regulatory framework, some stakeholders believe the community must continue to advance and evolve test development, validation, and quality assurance (QA) performance specifications, guided by current scientific knowledge and diagnostic capabilities to ensure consistent and accurate results for clinicians and patients.

In-silico sequence data sets and reference files (referred to herein as in-silico reference files, or I-SRFs)<sup>3</sup> are one possible avenue of advancement. Various stakeholders have employed I-SRFs to support diagnostic development and validation,<sup>4</sup> harmonization initiatives, and external QA activities, such as the diagnostic quality assurance pilot of the Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) working group.<sup>5</sup> Others have observed that compared with hard-to-obtain patient specimens or engineered wet-lab samples, customized I-SRFs cost less, are more versatile in design, and can assess bioinformatics performance across many types of genetic variants.<sup>6</sup>

In September 2022, a small subset of experts and stakeholders working to advance diagnostic quality convened to launch a working group to pragmatically consider the value of I-SRFs and options for expanding their application in a variety of potential use cases. Launch participants took stock of several in-silico-related initiatives to date and provided insights on the potential scope of the working group, which may add additional participants over time. Key points from these discussions are detailed in the following *Summary of Themes*.

## I-SRFs are already a recognized “tool in the toolbox” for validation and QA

Launch participants acknowledged that many institutions already recognize the value of I-SRFs in specific use cases. For example, new recommendations from the Association for Molecular Pathology and the College of American Pathologists (CAP) note that various types of I-SRFs can help validate laboratories’ bioinformatics pipelines and assess the performance of pipelines after software version changes or updates, especially when patient specimens may be limited.<sup>7</sup> The Food and Drug Administration has similarly noted I-SRFs’ added value as supplemental resources in assessing the performance of bioinformatics pipelines.<sup>8</sup> Other stakeholders, such as the CAP, employ I-SRFs in proficiency testing.<sup>9</sup> Additionally, the Centers for Disease Control and Prevention, in partnership with other stakeholders, is working on examining the role of I-SRFs for effective laboratory assessment of bioinformatics pipelines and is creating a curated list of variants for which an in-silico-based performance assessment may be useful.<sup>10</sup>

Participants also considered the limitations of in-silico approaches, specifically that I-SRFs only assess performance of bioinformatics pipelines and not the additional important preanalytical and postanalytical steps that laboratories perform when preparing and analyzing a sample. Some underscored that use of some types of I-SRFs, such as those employed in external proficiency testing, can be challenging for laboratories that lack the expertise to import and manage the large data files and workarounds necessitated by platform controls, as was observed in the SPOT/dx quality pilot.<sup>11</sup>

## A working group could seek to assess and progress opportunities for broader I-SRF utilization

Launch group participants also considered how a multistakeholder, precompetitive working group might explore or define expanded use of I-SRFs to advance and optimize the quality of biomarker-based diagnostics and treatments. A recent report described that while 36% of relevant laboratory professionals surveyed already use in-silico generated NGS data files to assess pipeline performance, technical limitations, updates, and assay validation, 46% of respondents were planning to but had not yet used in-silico data, and 18% were neither using nor planning to use it.<sup>12</sup>

During launch discussions, participants explored the following areas:

- **Application of in-silico files during clinical trials.** Some stakeholders were enthusiastic about possible use of in-silico files as standards to qualify and harmonize local laboratory partners and their assays when biopharmaceutical companies and others are conducting clinical trials. I-SRFs also may help with developing treatments and diagnostics for diseases with rare biomarkers for which there will never be sufficient clinical samples to conduct rigorous validation activities. One participant with experience with similar challenges

noted: *“It is just unimaginably hard to come up with a series of samples that you can use to do any kind of concordance testing [during trials]. It may not sound like it's difficult until you've actually tried to do it.”* Some participants felt these concepts merit further exploration, are aligned with prior recommendations from the drug and diagnostics industry and other stakeholders,<sup>13</sup> and could potentially increase community access to clinical trials.<sup>14</sup>

- **Integration of I-SRFs for assays in clinical use.** Of particular interest was how to pragmatically engage more stakeholders in the laboratory community to use I-SRFs to deepen their understanding of the performance of their assays on an ongoing basis for continued quality improvement, especially external QA. Some discussed initiatives that provide incentives to laboratories for using new external in-silico QA processes, such as renewing their in-network status with payers, as has recently been reported in the media.<sup>15</sup>

Overall, participants signaled there likely was value in both trial-oriented and clinical applications for I-SRFs, but more work is necessary to define and prioritize potential use cases beyond how I-SRFs are currently used today. A valuable next step could be to map out the use cases described above in more detail, likely in the form of a white paper. Such a paper could provide a foundation to help assess potential gaps and opportunities for expansion.

## Other potential focus topics await exploration

Launch participants discussed several other potential focus topics for the working group. For example, some raised the question of whether interpretation of variants should be part of the group's scope, with various perspectives offered. One who supported including interpretation in the group's scope said, *“If our end goal is about getting accurate answers for patients, interpretation must be part of this practice.”* Another noted, *“There's no way a laboratory can get the correct interpretation if they're not calling the variants correctly. And the thing that in-silico data sets can help with is understanding whether the bioinformatics can find the variants ... If you provide somebody with a mutagenized data set and if they don't find the variants, that's a question that can be addressed. It should be addressed independently from how labs would interpret the variants.”* Such diverse perspectives echo broader recent debates over whether oversight of variant interpretation infringes on pathology professionals' practice of medicine.<sup>16</sup> Finally, participants also discussed whether technical bottlenecks, such as the difficulties with file exchanges noted above, need to be discussed with commercial manufacturers and vendors before I-SRFs can be employed more broadly, concerns which align with recently released recommendations.<sup>17</sup> Whether the working group should take up this or any of the other potential focus topics is a matter for future discussion.

In addition to focusing on thematic topics, launch participants considered key principles for the working group, such as whether the group should prioritize speed or practicality over broader goals. Moving forward, the working group may continue to add and engage other

stakeholders for more in-depth discussions on shaping and prioritizing the various potential activities described above.

## About this document

This *Summary of Themes* reflects the use of a modified version of the Chatham House Rule whereby comments are not attributed to individuals, corporations, or institutions. Italicized quotations are comments made by participants before and during the meeting.

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## Participants

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- Center for Genomic Interpretation: Julie Eggington, Cofounder and CEO
- Centers for Disease Control and Prevention: Lisa Kalman, Health Scientist
- Emory University School of Medicine: Barbara Zehnbauser, Adjunct Professor of Pathology
- Friends of Cancer Research: Jeff Allen, President and CEO; Hillary Stires, Science Policy Analyst; Mark Stewart, VP, Science Policy
- Genomics Quality Assessment: Sandi Deans, Director; also NHS England, National Laboratory & Scientific Lead (Genomics)
- Gilead:\* Scott Patterson, VP, Biomarker Sciences; Tom Battersby, Senior Director, Biomarker IVD
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- Washington University School of Medicine: John Pfeifer, Vice Chair for Clinical Affairs, Pathology and Immunology, and former Quality Pilot Scientific Technical Working Group Chair

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## Endnotes

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- <sup>1</sup> Kathryn F. Mileham, Caroline Schenkel, Suanna S. Bruinooge et al., “[Defining Comprehensive Biomarker-Related Testing and Treatment Practices for Advanced Non-Small-Cell Lung Cancer: Results of a Survey of U.S. Oncologists](#),” *Cancer Medicine* 11, no. 2 (2022), 530–538.
- <sup>2</sup> “[Congress to Pass FDA User Fee Bill Without VALID Act, Again Putting Aside LDT Regulation](#),” *360 dx*, September 23, 2022.
- <sup>3</sup> The I-SRF acronym is not a formal name for the types of in-silico files described in this paper and in the various references provided below; it is being utilized on an interim basis. In time, the working group may adopt a different name, based on participant consensus, for the in-silico files and working group.
- <sup>4</sup> For a newly published primer on various types of I-SRFs and their use in assay validation, see: Eric J. Duncavage, Joshua F. Coleman, Monica E. de Baca et al., “[Recommendations for the Use of In silico Approaches for Next Generation Sequencing Bioinformatic Pipeline Validation: A Joint Report of the Association for Molecular Pathology, Association for Pathology Informatics, and College of American Pathologists](#),” *Journal of Molecular Diagnostics* Special Article (October 2022).
- <sup>5</sup> John D. Pfeifer, Robert Loberg, Catherine Lofton-Day et al., “[Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics](#),” *American Journal of Clinical Pathology* 157, no. 4 (April 2022), 628–638.
- <sup>6</sup> Tapestry Networks, *Addressing Lessons from the Diagnostic Quality Assurance Pilot*, Summary of Themes (Waltham, MA: Tapestry Networks, 2021), 5.
- <sup>7</sup> Duncavage et al., “[Recommendations for the Use of In silico Approaches for Next Generation Sequencing Bioinformatic Pipeline Validation: A Joint Report of the Association for Molecular Pathology, Association for Pathology Informatics, and College of American Pathologists](#).”
- <sup>8</sup> US Food and Drug Administration, *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases: Guidance for Stakeholders and Food and Drug Administration Staff* (Washington, DC: Food and Drug Administration, 2018), 24.
- <sup>9</sup> Duncavage et al., 18, and College of American Pathologists, “[New 2023 Surveys and Anatomic Pathology Education Programs](#),” accessed October 18, 2022.
- <sup>10</sup> Lisa V. Kalman and Ira M. Lubin, “[New CDC Partnerships to Advance the Development and Validation of Next Generation Sequencing Tests: A Publicly Available List of Expert Curated Variants](#),” *Genomics and Precision Health* (blog), November 16, 2021.
- <sup>11</sup> Pfeifer et al., “[Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics](#),” 5, 8.
- <sup>12</sup> Duncavage et al., 20.
- <sup>13</sup> Imein Bousnina, Megan Doyle, Maggie Huston et al., *Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications* (Friends of Cancer Research, 2022).
- <sup>14</sup> Janet Woodcock, Richardae Araujo, Twyla Thompson et al., “[Integrating Research into Community Practice — Toward Increased Diversity in Clinical Trials](#),” *New England Journal of Medicine* 385 (October 2021), 1351–1353.
- <sup>15</sup> Turna Ray, “[Highmark Asks Labs for Additional Validation Data on Cancer NGS Tests; Will Other Insurers Follow?](#)” *Precision Oncology News*, October 3, 2022; Turna Ray, “[Nonprofit's Efforts With Payors to Assess NGS Labs' Variant Interpretations Spark Debate](#),” *Precision Oncology News*, October 4, 2022.

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<sup>16</sup> For recent discussion on issues relating to variant detection versus variant interpretation, see Ray, [“Nonprofit’s Efforts With Payors to Assess NGS Labs’ Variant Interpretations Spark Debate.”](#)

<sup>17</sup> Duncavage et al., 27.